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OPEN Short Intensified Treatment in Children with Drug-susceptible Tuberculous Meningitis

To the Editors:

We read with interest the results of the study by van Toorn et al. describing short intensified treatment for children with drug-susceptible tuberculous meningitis (TBM).[1] The paper raises important questions regarding the most appropriate antimicrobial treatment regimen for children with TBM.

The World Health Organization (WHO) recommends giving 2 months of isoniazid, rifampin, pyrazinamide and ethambutol followed by 10 months of isoniazid and rifampin. After meningeal inflammation has subsided, rifampin has poor penetration into the cerebrospinal fluid (CSF)[2] leaving the child effectively on isoniazid monotherapy for most of their treatment. This can be a problem in areas with high prevalence of isoniazid resistance. In addition, the poor CSF penetration of ethambutol[2] renders its inclusion in the regimen questionable.

The short intensified treatment regimen used in the Western Cape for nearly 2 decades with higher isoniazid and rifampin dosages, longer administration of pyrazinamide and substitution of ethambutol with ethionamide provides higher CSF concentrations of anti-tuberculosis drugs for the entire duration of treatment.[2] It may also overcome isoniazid-monoresistance[3] and children appear to tolerate combination treatment with pyrazinamide better than adults.

Twelve years before the most recent WHO recommendations in 2010, this group published their experience with the same treatment regimen, showing that it was effective and associated with one of the lowest mortality rates reported.[4] It is disappointing that this regimen has not been evaluated further in other centers and that most authorities still recommend only 2 months of intensive treatment.

Despite demonstrating good outcomes and a shorter duration of treatment, the study by van Toorn is observational without a randomized control group for comparison; it thus may provide insufficient evidence to change international policy. In addition, the regimen employs a drug usually reserved for second-line treatment, which could have implications for acceptability by tuberculosis programs. Further, recent WHO dosing recommendations may make it difficult to use the higher dosages described in the study, given the shortage of single drug formulations in many settings.[5]

However, these operational obstacles should not impede the identification of the best possible treatment regimen. An appropriately powered randomized controlled trial to address this question is long overdue. One-hundred eighty-four children with TBM were enrolled in this study from a single center in 4 years; patient numbers, although limited, should not be an impediment to conducting a multicenter trial. Such a trial should compare the standard WHO-recommended regimen with a shortened regimen using drugs with good CSF penetration for the full duration. Consideration should be given to using a fluoroquinolone (levofloxacin or moxifloxacin) instead of ethionamide, as many pediatricians are hesitant to use ethionamide because of its side-effect profile as well as cross-resistance with isoniazid. Particular attention should be paid to using standardized assessments of neurologic outcome and toxicity and the issue of blinding. Until better evidence is provided, children with TBM will continue to be treated with what is likely to be a suboptimal regimen.

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In Reply: Short Intensified Treatment in Children With Drug-Susceptible Tuberculous Meningitis

Reply:

We agree with the North London TB journal club about the importance of trials that would determine the most appropriate antimicrobial regimen for children with tuberculous meningitis (TBM). The study design advocated by the authors is a randomized controlled trial (RCT) of short intensified versus standard treatment (as advised by the World Health Organization).

Although a RCT would be the preferred study method, a large sample size

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